Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial revisited ☆

This letter [1] raises many points echoing those already mentioned in other letters commenting on our paper [2]. To avoid redundancies with our responses to these letters, we will only answer here in a synthetic way. More detailed information can be found in our other response letters. Briefly, we confirm that we did not conduct a randomized, double-blind, placebo-controlled trial, since we consider such an approach unethical in the context of a potentially fatal infection like COVID-19, when preliminary data show that a treatment might be effective [3]. Control patients received standard of care treatment, including oxygen therapy when oxygen saturation was <92% and paracetamol in febrile patients. Possible adverse effects of hydroxychloroquine (HCQ) and azithromycin (AZ) were closely monitored by serum electrolyte analysis in patients with low serum potassium levels at baseline and by performing a routine electrocardiogram 48 hours after initiation of treatment. No cardiac effects were observed in patients included in this preliminary analysis. Since this study was conducted, we have treated a total of 3,119 COVID-19 patients with HCQ-AZ for at least three days. QTc prolongation (>60 ms) was observed in 25 patients (0.67%), resulting in discontinuation of treatment in 12 cases, including three cases with QTc> 500 ms. No cases of torsade de pointe or sudden death were observed [4]. We reanalyzed our data following the intention-to-treat concept, including all enrolled patients (n=42). Indeed, we estimated our results to be significant enough to stop the study before reaching the total number of patients initially calculated in our protocol (n=48). Analysis by intention-to-treat confirmed the effectiveness of HCQ-AZ on the reduction of viral load. In this updated analysis, we considered clinical outcomes, including the need for oxygen therapy, transfer to intensive care unit (ICU) and death. Requirement for oxygen therapy, transfer to ICU and death did not significantly differ between patients who received HCQ with or without AZ and controls with standard care only. We also calculated the length of hospital stay, which appeared to be significantly shortened in patients treated with HCQ alone, or HCQ and AZ, than in controls. We also used one-sided unconditional tests, including Barnard exact unconditional test and Wang exact 95% one sided-test, which appear to be more adapted in such a study with small sample sizes. The effectiveness of HCQ on the viral clearance of SARS-CoV-2 was confirmed using these tests. Regarding missing PCR data, results were considered positive if the results of PCR performed the day before and the day after were positive. Contrariwise, they were considered negative if the results of at least one of the previous two consecutive days were negative. We agree that most patients in our study presented with upper respiratory tract infection symptoms. We believe that HCQ-AZ treatment should be administered as early as possible in the course of the disease, before the onset of pneumonia symptoms. Such an early treatment proved to be effective in a larger study conducted at our institute on 3,737 COVID-19 patients, of which 3,119 (83.5%) were treated with HCQ-AZ for at least three days and 618 (16.5%) patients were treated with other regimens. Treatment with HCQ-AZ was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), a decreased risk of hospitalization ≥10 days (odds ratios 95% CI 0.38 0.27–0.54) and a shorter duration of viral shedding (time to negative PCR: HR 1.29 1.17–1.42) [4]. In this large retrospective observational study conducted in a single center, potential biases due to the inclusion of patients from other centers, as in our preliminary study, have been eliminated.

In conclusion, despite its limitations, weaknesses and imperfections, our study provided preliminary evidence that allowed us to treat a large number of patients with HCQ-AZ combination that was confirmed to be effective against COVID-19.

Declaration of Competing Interest

The authors declare no competing interests.

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Ethical approval

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